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EXAMINER	
NGUYEN, QUANG	

ART UNIT	PAPER NUMBER
1636	18

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/359,593	Applicant(s) GARVER ET AL.	
	Examiner Quang Nguyen, Ph.D	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If the period for reply specified above is less than thirty (30) days, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 4-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' amendment filed April 12, 2002 in Paper No. 17 has been entered.

Claims 1-2 and 4-49 are pending in the present application.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior office action.

Response to Amendment

The rejection of claims 1-2, 10 and 29 under 35 U.S.C. 102(e) by Russell-Jones et al. (U.S. Patent 6,159,502) is withdrawn in light of Applicants' amendment.

Claim Rejections - 35 USC § 112

Claims 32 (when read as a whole encompassing claims 30, 31), 34, 39, 17-20 (when read as a whole encompassing claims 15, 4, 2, 1) and 22 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons stated in the previous Office Action in Paper No. 10.

Claim 32 is directed to a method for delivering a nucleic acid into a cell comprising contacting a cell with a composition comprising a coacervate having limitations recited in claim 31, wherein the nucleic acid encodes a therapeutic agent, the cell is in a host and is transfected with the nucleic acid and express the therapeutic agent, and said agent produces a therapeutically beneficial response in said host.

Claim 34 is directed to a method for delivering a nucleic acid into a cell in a host comprising contacting a cell with a composition comprising a coacervate having limitations recited in claim 31, further comprising administering to said host said coacervate as a pharmaceutical composition. Claim 39 is directed to a method for preparing a pharmaceutical preparation, comprising combining a pharmaceutically acceptable excipient with a coacervate of cationic and anionic molecules, wherein a recombinant virus is encapsulated in said coacervate. Claims 17-20 and 22 are drawn to a composition of claim 15, wherein the microsphere when administered to a patient, provides controlled release of said expression vector.

The specification teaches by exemplification the preparation of microspheres made by the coacervation of gelatin and alginate in the presence of recombinant adenovirus containing a luciferase expression cassette. It further revealed that the variation in the microsphere composition and the cross-linking modulates the amount and released pattern of recombinant virus in *in vitro* assays. Lyophilization of adenovirus within the microspheres was also shown to minimize the bioactive loss in comparison to the lyophilization of free adenovirus. With a human lung cancer engrafted on nude mouse model, it was demonstrated that bioactive adenovirus were released *in vivo* from the microspheres that were injected intratumorally, as evident by the luciferase activity in harvested tumor nodules. The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instantly claimed invention because when read in light of the specification, it is drawn to methods for delivering a nucleic acid in the form of a coacervate to a cell in a host and for

preparing a pharmaceutical composition comprising a coacervate of the present invention for the purpose of gene therapy and/or nucleic acid immunization or for obtaining therapeutic effects in general (See page 3 of the specification, lines 1-5 and 17-19). With respect to claims 17-20 and 22, the only purpose for administering the composition of claim 15 into a patient is intended for obtaining therapeutic effects. As enablement requires the specification to teach how to make and use the claimed invention, the instant specification fails to enable the make and use of the methods and compositions as claimed.

Regarding to the gene therapy aspect of the claims, the specification is not enabled for the claimed invention because it fails to provide guidance for one skilled in the art on how to make and use the claimed methods and compositions to obtain any therapeutic effect contemplated by Applicants to treat a plethora of diseases, disorders or genetic defects such as Duchenne and Becker muscular dystrophy, adenosine deaminase deficiency, cancer, Parkinson's, Alzheimer's, AIDS among many others (specification, pages 39-41). There is no specific guidance as to promoters, vectors or dosages that are utilized to treat a particular disease, disorder or a genetic defect. Moreover, there is no correlation between the luciferase activity detected in harvested tumor nodules that had been treated with coacervate microspheres containing recombinant adenoviruses of this invention with the therapeutic results expected for the treatment of aforementioned diseases, disorders and genetic defects. As the art does not teach such a correlation nor provide such guidance, it is incumbent upon the specification to do so. Additionally, at the effective filing date of the present application,

gene therapy was still considered to be immature and highly unpredictable. Given the lack of guidance or direction provided by the instant specification, it would have required undue experimentation for one skilled in the art to make and use the claimed invention.

As noted in the previous Office Actions that there are several factors limiting an effective gene therapy, and these include sub-optimal vectors, the lack of a stable *in vivo* transgene expression, and most importantly an efficient gene delivery to target cells or tissues. The specification fails to provide teachings showing that a gene construct in the coacervate microsphere of the instant invention could provide an efficient therapeutic transgene expression in targeted cells or tissues that results in desirable treatment outcomes for any diseases contemplated Applicants. Wivel and Wilson (cited in the previous Office Action) noted that an efficient gene therapy vector has not existed, and regarding the failure of the instant specification to provide guidance for a skilled artisan on how to make and use an efficient gene therapy vector other than those already known in the art, it would have required undue experimentation for one skilled in the art to practice the instant claimed invention.

The claims also encompass the utilization of a nucleic acid encoding any therapeutic agents to be incorporated in the coacervate microspheres to treat aforementioned diseases, disorders and genetic defects. However, the specification fails to address issues such as the fate of delivering recombinant gene transfer vectors, the fraction of vectors taken up by targeted cells once they are released from coacervate microspheres, the level of mRNA produced, the stability of the recombinant protein produced, the recombinant protein's compartmentalization and its bioactive

activity. These factors differ dramatically based on which recombinant protein being produced to treat which disease or disorder, and the desired therapeutic effect being sought. Therefore, the level of gene expression, its duration and its *in vivo* therapeutic effects are not always predictable, and they can not be overcome by routine experimentation. With the lack of guidance and direction provided by the specification, it would have required undue experimentation for a skilled artisan to make and use the instant invention.

Regarding to the deliverance of a transgene encoding a therapeutic agent to a target cell in a host via coacervate microspheres, the specification fails to provide sufficient guidance or teachings on vector targeting to specific tissues or cells in the subject. At the effective filing, vector targeting *in vivo* to desired cells, tissues or organs continues to be unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller & Vile (FASEB 9:190-199, 1995) reviewed the types of vectors available for *in vivo* gene therapy, and concluded that ""for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances .... Targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (Exp. Opin. Ther. Patents 8:53-69, 1998) indicated that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain also reviewed new techniques under experimentation in the art

which show promise, but is currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma & Somia (Nature 389:239-242,1997) reviewed various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicated that at about the time of the claimed invention resolution to vector targeting had not been achieved in the art (see the entire article). Verma & Somia also discussed the role of the immune system in inhibiting the efficient targeting of viral vectors such that efficient expression is not achieved (see page 239, and second and third columns of page 242). Verma & Somia also indicated that appropriate enhancer-promoter sequences can improve expression, but that the "search for such combinations is a case of trial and error for a given cell type" (page 240, sentence bridging columns 2 and 3). The specification fails to provide sufficient guidance for a skilled artisan on how to overcome the unpredictability of vector targeting *in vivo*, such that an efficient gene transfer and expression could be achieved in specific target cells via coacervate microspheres in order to attain the desired therapeutic results.

With regard to the nucleic acid immunization aspect of the instant claims, the state of the art is new and unpredictable at the effective filing date of the present application. Chattergoon et al. (FASEB J. 11:753-763, 1997) stated that "Though DNA vaccines have shown promise in animal models and have raised hopes, the technology is considered an emerging technology" (column 1, paragraph 2, page 762) and "There is little evidence that the immune response induced by these vaccines will be completely protective against any human pathogen" (page 762, paragraph bridging

columns 1-2). Most recently, Leitner et al. (Vaccine 18:765-777, 2000) further stated "Although genetic vaccines have been significantly improved, they may not be sufficiently immunogenic for therapeutic vaccination of patients with infectious disease or cancer in clinical trials" (Abstract, page 765). Leitner et al. also listed several variable factors affecting the immunogenicity of genetic vaccines. These include: the structure of the plasmid backbone, amount of plasmid delivered, expression levels of the antigen, age and strain of the particular species, target tissue, and route of immunization among others (See Table 1, page 767). It is also recognized that the animal model should correlate to the disease conditions studied. Furthermore, it is impossible to predict whether an untested antigen of an infectious pathogen will elicit a protective immune response in a given type of animal and the route of administration was recognized as being a critical parameter determining whether protective immunity is elicited. Since the instant claims encompass any and all hosts, one skilled in the art has also recognized that results observed in animal model system following testing of a DNA expression vector-based agent are not predictive of outcome or efficacy in applications in other species of animal or in humans, due to differences in anatomy, cell biology, genetics, and immunology between different types of animals and between the animal models and humans. This is further supported by the teachings of McCluskie et al. (Mol. Med. 5:287-300, 1999) who stated "it is probably safe to say that any vaccine that works in a human will work in a mouse, but not necessarily vice versa. Therefore, it is difficult to predict from mouse studies the potential of a new vaccine for humans. In fact, in those human trials that have carried out, none of the DNA vaccines induced the strong

immune responses that had been seen in mice with the same vectors." (column 2, last paragraph, page 296). Against this background, the instant specification fails to provide any guidance demonstrating that the claimed methods of delivering a nucleic acid to a cell in a host via coacervate micropheres of the instant invention are effective for nucleic acid immunization purposes in any and all host for any and all diseases.

Additionally, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the unpredictability of gene therapy and nucleic acid immunization arts, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instantly claimed invention.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on June 28, 2001 in Paper No. 14 (pages 3-5) have been fully considered.

Applicants basically cited *In re Bran*. 51 F.3d 1560 (Fed. Cir. 1995) to support Applicants' assertions that sufficient advancement in the technology of gene therapy existed at the time of filing to support enablement of even gene therapeutic applications of the claimed invention.

Applicants' arguments are respectfully found unpersuasive because the instant claims are not drawn to anti-tumor compounds, but to a gene therapy method using the gene delivery composition of the presently claimed invention, and that the rejection is not made for the lack of utility but for enablement issue. Therefore, the cited *In re Bran* case law is not relevant. Applicants' assertion is contrary to the state of the gene therapy art and genetic immunization, particularly for attaining therapeutic effects as reflected by the references cited by Examiner. To further support examiner's position, with respect to the issue of gene therapy and translational cancer research Dang et al. (Clin. Cancer Res. 5:471-474, 1999; Cited previously) stated "This workshop reviewed some recent advances in gene delivery, gene expression, immune manipulation, and the development of molecular targets and stressed that <u>all of these fields will need further advancement to make gene therapy a reality</u>" (page 471, col. 1, bottom of first full paragraph). If obtaining therapeutic effects via gene therapy is not a reality in 1999, then why would one reasonably expect to obtain desired therapeutic results contemplated by Applicants via the claimed methods at the effective filing date

(7/23/1998) simply based on the guidance provided by the instant specification and Applicants' assertions?

With respect to composition claims, Applicants argued that the requirement of 35 U.S.C. 112, first paragraph do not include that all conceivable uses of the claimed composition be enabled. In this case, Applicants argued that Applicants have supported numerous uses of the claimed invention (e.g., delivery of a toxin for killing undesirable cells, DNA vaccination, for imaging, for transformation of cells *in vitro* for *ex vivo* gene therapy applications). Applicants' arguments are respectfully found unpersuasive the only purpose for administering the composition of claim 15 into a patient is intended for obtaining therapeutic effects (a pharmaceutical composition), and the composition is not used for imaging or for *in vitro* transformation of cells for ex vivo gene therapy applications. Furthermore, the expression of an antigen or a recombinant by an expression vector in the composition of claim 17 administered to a patient would not enable one for imaging anything as asserted by Applicants for use other than gene therapy or genetic vaccination in a patient. With the lack of guidance provided by the instant specification, it would have required undue experimentation for a skilled artisan to make and use the instant claimed compositions for the reasons already set forth above.

Accordingly, the claims remain rejected under 35 U.S.C. 112, first paragraph for the reasons set forth above.

Amended claims 1-2, 4-10, 13-16, 21, 23-31, 33, 35 and 40-49 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition for controlled release of a nucleic acid comprising a coacervate microsphere encapsulates a nucleic acid associated with a delivery agent, wherein the coacervate microsphere comprises a polycation molecule and a polyanionic molecule, a gene delivery system or a kit comprising the same and a method for delivering a nucleic acid molecule into a cell using the same, does not reasonably provide enablement for other embodiments of the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action in Paper No. 15 (pages 11-14).

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on June 28, 2001 in Paper No. 14 (pages 5-6) have been fully considered.

Applicants basically argued that any different numbers of anionic and cationic polymers are capable of forming complex coacervates that are effective for delivery to mammalian cells as evidenced by the cited references of Matthew et al., Kaibara et al. and Burgess et al. Applicants' argument is found unpersuasive because it is noted that the claims do not limit to the making and using a coacervate microsphere for controlled release of a nucleic acid, or the coacervate comprises of a polyanionic molecule and a polycationic molecule, rather they encompass a coacervate comprising any cationic

molecule and any anionic molecule. The cited references do not support for the making and using of any coacervate composed of any cationic molecule and any anionic molecule, or in any form other than microsphere or microcapsule.

Claim Rejections - 35 USC § 103

Amended claims 1-2, 4-5, 10-20, 23-31, 33-39 and 48 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Russell-Jones et al. (U.S. Patent No. 6,159,502) in view of Beer et al. (Adv. Drug Delivery Reviews 27:59-66, 1997; Cited previously).

The claims are drawn to a composition for controlled release of a nucleic acid comprising (a) a coacervate, (b) a nucleic acid incorporated in said coacervate, and (c) a delivery agent incorporated in said coacervate, wherein the coacervate comprises a cationic molecule and an anionic molecule other than said nucleic acid and the delivery agent is other than said cationic molecule of the coacervate; the same composition with various limitations recited in dependent claims; a gene delivery system comprising the same, a kit containing the same gene delivery system and a method for delivering a nucleic acid into a cell using the same gene delivery system.

With respect to the composition claims 17-20, the intended use of the composition is not given any patentable weight in view of the prior art. With respect to claims 34 and 39, the pharmaceutical composition or preparation is interpreted as a composition or preparation containing a pharmaceutically acceptable excipient, and not for the intended pharmaceutical use. Within the enabled scope of the instant claimed

invention, Russell-Jones et al. disclose the preparation for complexes and compositions for oral delivery of a substance or substances to the circulation or lymphatic drainage system of a host. The complexes comprise a microparticle or microsphere coupled to at least one carrier, the carrier being capable of enabling the complex to be transported to the circulation or lymphatic drainage system via the mucosal epithelium of the host, and the microparticle or microsphere being capable of encapsulating the substances (See abstract). Specifically, Russell-Jones et al. teach that the microsphere can be made by complex coacervation include mixtures of polyanions, such as gum arabic, alginate, carboxymethyl cellulose, heparin sulphate among others with polycations of polylysine and gelatin (col. 10, lines 16-22). Russell-Jones et al. further teach that the microsphere encapsulates DNA or RNA or ribozyme (col. 6, lines 35-45 and the claims). Russell-Jones et al. also teach that the microspheres have size from 1 nanometer to 100 micrometers in diameters, and they can be prepared by a number of well known methods apart from the complex coacervation for encapsulation a desired substance, (col. 2 and col. 4, lines 39-42). Additionally, the disclosed complex or composition can be mixed with a pharmaceutically acceptable carrier, diluent, excipient and or adjuvant (col. 14, lines 7-14). Russell-Jones et al. also teach a method of orally delivering a substance, such as DNA, RNA or ribozymes to the circulation or lymphatic drainage system of a host by orally administering to the host the complex comprising the microsphere and wherein the substance is released from the microsphere when the complex enters the circulation or lymphatic drainage system of a host (See examples 13, 14 and the claims). Additionally, Russell-Jones et al. also disclose a kit comprising

a plurality of different carriers and a plurality of different microparticles or microspheres containing the same or different substance of interest to prepare a complex for oral delivery (col. 6, lines 64-67). However, Russel-Jones et al. do not specifically teach the encapsulated DNA is in the form of a recombinant viral vector, wherein the nucleic acid is a viral vector and the delivery agent is a virus of said viral vector.

Beer et al. disclosed a composition of poly (lactic-glycolic) acid (PLGA) microspheres containing a recombinant adenovirus, AdRSVntlacZ. Upon injection into the striatum of mice with microspheres containing AdRSVntlacZ, beta-galactosidase activity was detected in harvested brains after 7 days, and a dose dependent increase in beta-galactosidase activity was also noted (see Fig. 4). Although viable virus could be delivered both *in vitro* and *in vivo* from the PLGA microspheres, optimal microencapsulation yield, virus stability, and efficient transfer remained elusive (second column, second paragraph, page 63). Beer et al. suggested that different polymers should be investigated for their ability to allow for sustained release of recombinant viral vectors (column 2, last paragraph, page 63). It should be noted that beta-galactosidase is also an antigen upon administering into a host.

Accordingly, it would have been obvious and within the scope of skill for an ordinary skilled artisan at the time of invention was made to encapsulate the recombinant adenoviral virus into a microsphere composition taught by Russell-Jones et al. in light of the teachings of Beer et al. One of ordinary skilled artisan would have been motivated to carry out such modification to improve the microencapsulation yield and virus stability in a microsphere in order to improve the efficiency of gene delivery

(Beer et al., page 63, column 2, first full paragraph), particularly for a composition suitable for oral delivery of a substance to the circulation or lymphatic drainage system of a host as one taught by Russell-Jones et al. Beer et al. suggested that other methods and different polymers should be investigated for their ability to allow sustained release of recombinant viral vectors (column 2, last paragraph, page 63). A kit comprising the modified microsphere resulting from the combined teachings of Russell-Jones et al. and Beer et al. would have been obvious, as well as a method for delivering a nucleic acid to a cell using the modified microsphere. With respect to claim 16 reciting the incorporated virus comprising at least about five percent by weight of the microsphere, this would have been within the scope of skills of an ordinary artisan at the time of the instant invention to prepare the modified microsphere having such limitation. It is further noted that this is not the novel aspect of the present invention.

Thus, the claimed invention as a whole was *prima facie* obvious in the absence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on April 12, 2002 in Paper No. 17 (page 9) have been fully considered.

Applicants argued that the amended claims 1 and 29 serve to distinguish the instant invention from the cited art. Additionally, Applicants argued that the asserted combination of Russell-Jones et al. with Beer et al. suffers from the defects of record noted in the response to the previous Office Action in which Truong et al. (U.S.

6,025,337) in view of Beer et al. Basically, Applicants previously argued that the combination of the teachings of Truong et al. and Beer et al. do not meet all the claim limitation, and that there would not have been a reasonable expectation of success or sufficient motivation to combine the reference (Amendment filed June 28, 2001, page 9).

Applicants' arguments are found unpersuasive because unlike the combination of Truong et al. and Beer et al., the combined teachings of Russell-Jones et al. and Beer et al. meet all the limitations of the amended claims. Applicants have failed to point out which features of the presently claimed invention that the aforementioned combined teachings do not teach. One of ordinary skilled artisan would have been motivated to carry out the aforementioned modification to improve the microencapsulation yield and virus stability in the microsphere composition of Beer et al. in order to improve the efficiency of gene delivery (Beer et al., page 63, column 2, first full paragraph), particularly for a composition suitable for oral delivery of a substance to the circulation or lymphatic drainage system of a host. Beer et al. suggested that other methods and different polymers should be investigated for their ability to allow sustained release of recombinant viral vectors (column 2, last paragraph, page 63). Additionally, Russell-Jones et al. note apart from the coacervation process, there are several well known methods available for preparing microspheres to encapsulate the desired substance. Applicants have not provided any factual evidence or any scientific reasoning why the combined teachings would not have a reasonable expectation of success.

Accordingly, amended claims 1-2, 4-5, 10-20, 23-31, 33-39 and 48 remain rejected for the reasons set forth above.

Claims 40-47 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Russell-Jones et al. (U.S. Patent No. 6,159,502) in view of Beer et al. (Adv. Drug Delivery Reviews 27:59-66, 1997; Cited previously) as applied to claims 1-2, 4-5, 10-20, 23-31, 33-39 and 48 above, and further in view of Leong et al. (U.S. Patent No. 5,759,582, PTO-1449 # 6, AB).

The claims are drawn to a method for preparing a gene delivery system in which the microspheres prepared from the coarcevation of a cationic molecule and an anionic molecule encapsulate a nucleic acid, preferably a recombinant virus, and a coacervate microsphere for transfection and expression of a recombinant protein prepared from the same method.

The teachings of Russell-Jones et al. and Beer et al. and the motivation for their combined teachings have been presented above. Neither references specifically discloses method steps for preparing the modified microsphere encapsulating a recombinant adenvirus resulting from the combined teachings of Russell-Jones et al. and Beer et al. Although Russell-Jones et al. teach that DNA or RNA or ribozyme can be encapsulated in a microsphere prepared by complex coacervation between mixtures of polyanions, such as gum arabic, alginate, carboxymethyl cellulose among others with polycations of polylysine and gelatin (col. 10, lines 16-22 and the claims), they do not specifically disclose the method steps, presumably the process of forming a

microsphere prepared from a complex coacervation is well known. At the effective filing date of the present application, Leong et al. (US Patent No. 5,759,582) taught a method for preparing a pharmaceutical composition in the form of a coacervate microsphere, comprising the following steps: (a) providing a gelatin (a cationic molecule) aqueous solution; (b) providing a chondroitin sulfate (an anionic molecule) aqueous solution; (c) adding a therapeutically effective amount of a pharmaceutically active substance either to the solution in step (a) or to the solution in step (b); (d) mixing the gelatin and chondroitin sulfate solutions to form a coacervate suspension; (e) adding a crosslinking agent to the coacervate suspension to crosslink the coacervates, the coacervates encapsulating the pharmaceutically active substance; and (f) incubating the coacervate suspension to form microspheres and recovering the microspheres. (col. 2 in summary of invention). Leong et al. further taught that after recovering the microspheres, they may be washed and dried in a standard techniques, e.g., lyophilization (col. 4, last paragraph).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to modify a method of preparing a coarcevate microsphere disclosed by Leong et al. (US Patent No. 5,759,582) in light of the combined teachings of Russell-Jones et al. and Beer et al., by substituting a pharmaceutical composition comprising water soluble protein, peptide, glycoprotein, or mixture thereof in step (c) with a recombinant adenovirus in order to obtain the modified microsphere that encapsulates a recombinant adenovirus. The motivation for one of

ordinary skilled artisan to carry out the above modification are already discussed in the rejection of claims 1-2, 4-5, 10-20, 23-31, 33-39 and 48 above.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on April 12, 2002 in Paper No. 17 (page 9) have been fully considered.

Applicants argued that the asserted combination of Russell-Jones et al. with Beer et al. and Leong et al. suffers from the defects of record noted in the response to the previous Office Action in which claims 40-47 were rejected under 35 U.S.C. 103(a) as being unpatentable over Leong et al. in view of Truong et al. and Beer et al. Basically, Applicants previously argued that the combined references fail to provide sufficient motivation to combine them, and there would have been no reasonable expectation of success to obtain the claimed invention, but mainly the modified microsphere resulting from the combined teachings of Truong et al. and Beer et al., a coacervate would not be formed because the nucleic acid of the recombinant virus is in the viral particle (Amendment filed June 28, 2001, pages 10-12). Applicants' arguments are found unpersuasive for the following reasons.

Firstly, unlike the reference of Truong et al. which teaches the preparation of a coacervate of gelatin and nucleic acid, wherein a nucleic acid acts as a polyanionic molecule; Russell-Jones et al. clearly teach that the microsphere can be made by

complex coacervation include mixtures of polyanions, such as gum arabic, alginate, carboxymethyl cellulose, heparin sulphate among others with polycations of polylysine and gelatin (col. 10, lines 16-22). Russell-Jones et al. further teach that the microsphere encapsulates DNA or RNA or ribozyme (col. 6, lines 35-45 and the claims).

Secondly, as already discussed above, one of ordinary skilled artisan would have been motivated to carry out the modification to improve the microencapsulation yield and virus stability in the microsphere composition of Beer et al. in order to improve the efficiency of gene delivery (Beer et al., page 63, column 2, first full paragraph), particularly for a composition suitable for oral delivery of a substance to the circulation or lymphatic drainage system of a host as one taught by Russel-Jones et al. Beer et al. suggested that other methods and different polymers should be investigated for their ability to allow sustained release of recombinant viral vectors (column 2, last paragraph, page 63).

Thirdly, Applicants have not provided any factual evidence or any scientific reasoning why the combined teachings would not have a reasonable expectation of success.

Accordingly, the claims remain rejected for the reasons set forth above.

Amended claims 1-6, 10-15, 17, 22 and 49 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Russell-Jones et al. (U.S. Patent No. 6,159,502) in view of McElligott et al. (WO 94/23738, PTO-1449#6, AK).

The claims are drawn to a composition for controlled release of a nucleic acid comprising (a) a coacervate, (b) a nucleic acid incorporated in said coacervate, and (c) a delivery agent incorporated in said coacervate, wherein the coacervate comprises a cationic molecule and an anionic molecule other than said nucleic acid and the delivery agent is other than said cationic molecule of the coacervate; the same composition with various limitations recited in the dependent claims.

With respect to composition claims 17 and 22, the intended use of the composition is not given any patentable weight in view of the prior art. Within the enabled scope of the instant claimed invention, Russell-Jones et al. disclose the preparation for complexes and compositions for oral delivery of a substance or substances to the circulation or lymphatic drainage system of a host. The complexes comprise a microparticle or microsphere coupled to at least one carrier, the carrier being capable of enabling the complex to be transported to the circulation or lymphatic drainage system via the mucosal epithelium of the host, and the microparticle or microsphere being capable of encapsulating the substances (See abstract). Specifically, Russell-Jones et al. teach that the microsphere can be made by complex coacervation include mixtures of polyanions, such as gum arabic, alginate, carboxymethyl cellulose, heparin sulphate among others with polycations of polylysine and gelatin (col. 10, lines 16-22). Russell-Jones et al. further teach that the microsphere encapsulates DNA or RNA or ribozyme (col. 6, lines 35-45 and the claims). However, Russell-Jones et al. do not specifically teach that the encapsulated DNA is in the form of a recombinant transfer vector, or the encapsulated DNA is associated with

any delivery agent or that the disclosed microsphere comprises a second expression vector.

At the effective filing date of the present application, McElligott et al. teach that DNA or RNA molecules can be conjugated by way of chemical bonds with promoting material which promotes the uptake or the transport to the nucleus of cells, such as fatty acids, phospholipids, glycolipids among others (Summary of the invention), and that the conjugated genetic material can be encapsulated in a microsphere suitable for the controlled release of the nucleic acid molecule to a target cell (Summary of the invention). The microsphere can be prepared by various methods available in the art (pages 15-26). McElligott et al. further teach that encapsulation of genetic material would protect the nucleotides from enzymatic degradation before they are released, and that controlled release of genes would also reduce lethality to the host by allowing controlled expression of the product (page 4, lines 3-7). Specifically, McElligott et al. disclosed various plasmid expression vectors having a promoter, regulatory region along with the coding region of specific nucleotide sequence encoding for the desired gene product, including cytokines or gene product killing cancer cells (page 9, lines 20-24; page 28, col. 20-22 and examples 1, 5).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to incorporate DNA or RNA in the form of a plasmid expression vector conjugate as taught by McElligott et al. into the microsphere composition disclosed by Russell-Jones et al. One of ordinary skilled in the art would have been motivated to carry out the above modification, because the DNA in the form

of a conjugate facilitates the uptake and integration of the genetic material into cells upon being released from the microsphere as taught by McElligott et al. With respect to claim 22 reciting further comprising a second expression vector, it would have been obvious and a matter of choice for an investigator to have two different expression vectors being encapsulated into the same microsphere.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on April 12, 2002 in Paper No. 17 (page 10) have been fully considered.

Applicants mainly argued that the asserted combination of Russell-Jones et al. with McElligot et al. suffers from several of the defects of record in the art cited under 103 U.S.C. 103(a) as noted in the response to the previous Office Action. Additionally, Applicants argued that McElligot et al. repeatedly recite the feature that the nucleic acid be conjugated to the "promoting material" by way of chemical bonds...which promotes the uptake or the transport, and therefore the teachings of McElligot et al. would lead the skilled artisan away from making substitutions of the essential features with the microsphere formulations of Russell-Jones et al. Applicants' arguments are respectfully found to be unpersuasive for the following reasons.

Firstly, Examiner is not clear which defects regarding to the combined teachings of Russell-Jones et al. (U.S. Patent No. 6,159,502) in view of McElligott et al. (WO

94/23738, PTO-1449#6, AK) in the previous Office Action that Applicants refer to. Please note that Applicants have not specifically address the defects of this combination of references in any of the previous Office Action.

Secondly, McEllitott et al. teach the nucleic acid conjugated by way of chemical bonds with promoting material (e.g., glycoproteins, lipoproteins, antibodies, proteinaceous cellular ligands, fatty acids, cholesterol, triglycerides, phospholipids) which promotes the uptake or the transport to the nucleus, or expression of the nucleic acid in the cell (page 5, lines second full paragraph). The promoting material falls within the definition of a delivery agent that is defined by the presently claimed invention as a molecule that facilitates the intracellular delivery of a bioactive substance such as sterols, cholesterol and others (see page 9, lines 5-13). McElligott et al. further teach that encapsulation of genetic material would protect the nucleotides from enzymatic degradation before they are released, and that controlled release of genes would also reduce lethality to the host by allowing controlled expression of the product (page 4, lines 3-7). Therefore, there is nowhere in the reference of McElligott et al. that one can find negative teachings with respect to why one should not encapsulate a conjugated nucleic acid in a coarcevate microsphere taught by Russell-Jones et al., particularly McElligott et al. specifically teach that the nucleic acid material should be encapsulated to protect the nucleotides from enzymatic degradation before they are released.

Accordingly, the claims remain rejected for the reasons set forth above.

Amended claims 1, 2 and 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Russell-Jones et al. (U.S. Patent No. 6,159,502) in view of McElligott et al. (WO 94/23738, PTO-1449#6, AK) as applied to claims 1-6, 10-15, 17, 22 and 49 above, and further in view of Leong et al. (U.S. Patent No. 5,759,582, PTO-1449 # 6, AB) and Gombotz et al. (U.S. Patent No. 5,942,253).

The claims are drawn to a composition for controlled release of a nucleic acid comprising (a) a coacervate, (b) a nucleic acid incorporated in said coacervate, and (c) a delivery agent incorporated in said coacervate, wherein the coacervate comprises a cationic molecule and an anionic molecule other than said nucleic acid and the delivery agent is other than said cationic molecule of the coacervate; the same composition wherein said coacervate is a microsphere and wherein the microsphere is crosslinked by a crosslinking agent, preferably a metal cation and more preferably calcium.

The teachings of Russell-Jones et al. and McElligott et al. and the motivation for their combined teachings have been presented above. Neither references specifically teaches that the modified microsphere can be crosslinked by a crosslinking agent, preferably a metal ion and more preferably calcium ions. However, at the effective filing date of the present application, it is known that a coacervate microsphere can be crosslinked to reinforce the encapsulation of the active substance as taught by Leong et al. (col. 3, lines 63-65), and that glutaraldehyde can be used as a crosslinking agent for a coacervate of gelatin and chondroitin sulfate (col. 4, lines 17-19). Additionally, in teaching the preparation of a microsphere for a controlled and prolonged release of GM-CSF orally to a host, Gombotz et al. disclose that alginate in a hydrogel microsphere

can be ionically cross-linked with divalent ions such as calcium (col. 6, lines 14-22; col. 8, line 66 continues to line 6 of col. 9).

Accordingly, it would have been obvious to a person of ordinary skill in the art at the time of invention was made to crosslink the modified microsphere composition resulting from the combined teachings of Russell-Jones et al. and McElligott et al. with crosslinking agents such as glutaraldehyde or calcium ions (for coacervate involving alginate as a polyanion) in light of the teachings of Leong et al. and Gombotz et al. One of ordinary skilled in the art would have been motivated to carry out the above modification to reinforce the encapsulation of the bioactive substance, for this instance the conjugated-DNA complex, or the overall stability of the modified microsphere as taught by Leong et al.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

Applicants' arguments related to the above rejection in the Amendment filed on April 12, 2002 in Paper No. 17 (page 10) have been fully considered.

Applicants presented the same arguments as those in response to the rejection of claims 1-6, 10-15, 17, 22 and 49 above. Applicants' arguments are respectfully found unpersuasive for the same reasons set forth above.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

Quang Nguyen, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER